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<p>(21) International Application Number: PCT/DK91/00012 (22) International Filing Date: 18 January 1991 (18.01.91) (30) Priority data: 0178/90 22 January 1990 (22.01.90) DK (71) Applicant (for all designated States except US): NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK). (72) Inventor; and (75) Inventor/Applicant (for US only) : BONNICHSEN, Frits [DK/DK]; Hoejdevvej 31, DK-3540 Lyngbe (DK). (74) Common Representative: NOVO NORDISK A/S; Patent Department, Novo Allé, DK-2880 Bagsvaerd (DK).</p>		<p>(81) Designated States: AT, AT (European patent), AU, BE (European patent), BG, BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, RO, SE (European patent), SU, US. Published <i>With international search report.</i></p>
<p>(54) Title: A PROCESS AND APPARATUS FOR MIXING AND INJECTING A MEDICINE</p> <div data-bbox="318 1129 1299 1701"> </div> <p>(57) Abstract</p> <p>To ensure the most careful mixing of the liquid and the dry phase in a two-compartment carpule (1) this carpule (1) is placed in a housing (17) and secured by mounting a needle (19). A piston rod (9) may then be passed forward to mix the medicine, this mixing being obtained by a uniform forwards movement of the piston rod, air in the mixing chamber being let out through the needle (19). For subsequent setting a dose of the mixed medicine to be injected, the movement of the piston may be preset by separating through a threaded connection (26) a press part (10, 20) from the piston rod (9). By this separation the movement of the piston rod (9) is restricted during the injection and consequently the injected dose is limited.</p>		

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A PROCESS AND APPARATUS FOR MIXING AND INJECTING A MEDICINE

The invention concerns a process for mixing a liquid and a medicament in a two-compartment carpule after this carpule has been positioned in a syringe for dosed injection of
5 the mixed product, the carpule comprising a front chamber containing the medicament and being at its front end delimited by a membrane closing the front end of the carpule and being at its rear end closed by a first displaceable piston, and a rear chamber containing the liquid and being at its front end
10 delimited by the first displaceable piston and being at its rear end delimited by a second displaceable piston at the rear end of the carpule, and a passage between the two chambers, which passage may be opened by a joint displacement of the first and the second piston and the liquid between them in a
15 direction towards the front end of the carpule, whereafter a further displacement of the second piston presses the liquid through the passage for mixing with the medicament.

The invention further concerns an apparatus which allows the performance of this process and which is usable for
20 subsequent dosed injection of the mixture.

Processes and apparatus of this kind are particularly used for ambulatory treatment as the patient himself can mix the medicine before it is injected.

Particularly by easily decomposable medicine substances, these may advantageously be packaged in a two-compartment
25 carpule, whereby the shelf life will be extended considerably.

An example of such a medicine may be a freeze-dried growth hormone which cannot stand vigorous shaking when mixed, and consequently the mixing should take place shortly before
30 the injection and as carefully as ever possible.

From the specification of Danish Patent Application No. 3679/88 a process for mixing such a medicine and an injection device therefor is known.

The mixing is performed by the rear piston being
35 moved forwardly in the rear chamber by a screw mechanism pressing the liquid-containing phase into the front chamber

with the sensitive phase under a relatively high pressure, and thus the mixing is carried out under pressure in the closed front chamber.

The spiral movement is performed by rotating a button 5 at the end of the device by the fingers, which means that the spiral movement will take place jerkily. This will inevitably disturb the mixing, both as regards shakings and as regards the admission of liquid. Furthermore, the mixing takes place under pressure as the carpule is sealed by a membrane, which produces 10 unwanted mixing whirls in the mixture.

It is the object of the invention to remedy these deficiencies and disadvantages of the known methods, which is obtained by inserting the carpule in a tubular housing from the front end thereof, so that a piston rod mounted in the housing 15 and being displaceable in the longitudinal direction thereof is pressed out through the rear end of the housing by abutting the second piston whereupon a screw stopper carrying a needle is mounted to secure the carpule in the housing and penetrate the membrane, whereafter the piston rod is pressed into the housing 20 to press the rear piston forwards in a direction towards the front end of the carpule until the liquid has been pressed through the passage into the front chamber.

Hereby a particularly careful mixing is obtained, primarily as the forward movement of the piston rod will be a 25 continuous motion, i.e. without breaks when the piston rod is moved forward, e.g. when pushed against a tabletop or the like. This method also provides a better mixing as it is carried out at the same time as the pressure is releaved through the needle and at constant admission of liquid. Thus, this methods differs 30 from the methods known in the art by shakings, pressure, and unwanted variations in the admission of liquid being totally avoided. This provides a hitherto unknown and good shelf life of the mixture and thus the optimal treatment.

As mentioned in claim 3, by providing the piston rod 35 in a mixing and injecting apparatus with a withdrawal detent the risk of unintended inlet of air by withdrawal, e.g. when setting the dose, is averted.

As mentioned in claim 4, by providing the apparatus with a setting mechanism for determining the forward movement of the piston rod during injection, an accurate dosing and consequently an optimal medical treatment is obtained.

5 As mentioned in claim 5, by providing the setting mechanism with a scale which is set to zero after each injection the risk of incorrect dosing will be reduced.

As mentioned in claim 6, by preventing the piston rod from rotating when setting the dose, injection of the exact
10 amount is insured.

Finally, as referred to in claim 7, it is appropriate to design the withdrawal detent and the coupling as holders having arms with teeth engaging backwards facing teeth on the piston rod whereby the piston rod on one side is prevented from
15 being passed backwards when the arms are pressed against the piston rod, and on the other side is prevented from being rotated when the holders engage longitudinal tracks in the piston rod.

The invention will now be described in further
20 details with reference to the drawing in which

Fig. 1 shows a sectional view of an injecting apparatus for manual needle insertion, and where the mixing is completed and the apparatus is ready for setting and
25 injection, and

Fig. 2 shows a sectional view of an injecting apparatus for automatic needle insertion, where the mixing is completed too, and where the apparatus is ready for setting
30 and injection.

On the drawing two embodiments of the apparatus according to the invention are shown as examples of preferred embodiments.

Referring to Fig. 1 a so-called manual mixing and
35 injecting pen will be described in further details below.

The two-compartment carpule 1 when in its standard storing condition is divided into two compartments, the liquid

phase being in the rear chamber, and the medicine phase in the front chamber.

The piston 24 is in a position behind the passage between the two chambers, and the rear piston 23 is at the rear 5 of the carpule 1. At its front the carpule is provided with a membrane and a holder for the needle 19, which needle is, however, usually not mounted until after the carpule has been inserted in the house 17 of the pen.

The house 17 has the form of a tubular case, wherein 10 the carpule 1 can be inserted from the right in the drawing. When the carpule 1 has been inserted it is secured by screwing into the house from the front thereof a locking member 16 with the needle 19 penetrating the membrane.

Behind the carpule 1 a thrust collar 3 has been 15 situated, which thrust collar is provided with a smaller thrust collar which is passed backwards into the house when the carpule 1 is inserted.

From the enlarged detail drawing it furthermore appears that at its back the house 17 is designed with a case 20 member 8, wherein a locking device 28 having elastic detent arms 4 is mounted. These arms 4 normally extend in axial direction and are at their under side at their ends provided with a cogging sloping forwards.

When during insertion the carpule 1 is pressed 25 against the thrust collar 3, the arms 4 are pressed downwards when the carpule is pressed home, and the teeth pass into a barrier mesh with corresponding teeth 25 provided on the outer side of a piston rod 9.

This mesh functions as a oneway detent as the piston 30 rod 9 will then be forwards slidable, but never backwards, thus making suction of air impossible.

The piston 9 is furthermore prevented from rotating about its longitudinal axis, as the arms 4 or the locking device 28 functions as a pawl in a longitudinal track 29 in the 35 piston rod 9, so that the piston rod is made unrotatable, which is necessary in order to accomplish a setting of the dose by a rotational movement.

As appears from the drawing, the piston rod 9 projects over the house 17 and is at its end provided with a thread which can be placed inside, as shown, or outside.

Into this inside thread is screwed a threaded member 5 26, being at its end fixed to a bottom 20 which extends outside in a cap 10, which again runs outside on the case member 8 of the house 17.

The rear of the case member 8 is provided with a click arm 11 which works with inside longitudinal grooves in 10 the cap 10, and the axial movement of the cap is delimited by these grooves, the grooves providing a stop 21 delimiting the longitudinal displacement of the cap 10.

Finally, a scale 7 actuated by a circumferential spring 12 is mounted, so that when setting the dose by rotating 15 the cap 10, 20, the scale 7 may be detained against a non-shown stop. The scale is released when pulling back the cap, whereby the spring turns the scale to its initial position.

The dosing is set by rotating the cap and is marked by the number of clicks from the click arm 11, thus unscrewing 20 the cap 20 from the piston rod 9. At the same time the scale is rotated in such a way that the dose may be read as compared to a zero on the house 17. Then the injection is carried out by pressing forward the cap 20 until the injection is finished, i.e. when the cap 20 abuts on the case 8. Hereafter the cap 10 25 is passed back zeroing the scale 7, and a new dose may be set and injected.

The scale further has a stop 22 on the case 8 making it possible to limit the movement and thereby the set dose, the movement of the case 8 in the longitudinal direction being 30 limited.

On Fig. 2 is shown an example of an embodiment where the apparatus is also provided with a spring-driven needle insertion device.

In the house 17 there is also a chamber for the 35 carpule 1, so that it can be inserted from the end and thus influence the thrust collar 3 which again will actuate the detent arms 4 to be thrown into mesh with the teeth 25 of the

The mixing is performed by screwing the cap 10 down against the end of the piston rod as shown in the drawing, and by holding the pen in a vertical position and placing the cap in abutment against e.g. a table top the cap may be pressed 5 gently inwardly until it is flush with the house. The mixing is now finished, the pistons 23, 24 being situated abreast of the passage as shown in the drawing.

Referring to Fig. 2, the injection will now be explained.

10 A cap 18 protecting the needle 19 is pressed inwards. Hereby the spring 14 is compressed and the hook 5 engages the locking member 6. At the same time the cap 10 engages the scale 7 and a presetting may be performed by rotating the cap relative to the piston rod 9. During this rotation the ball 15 lock 11 clicks into the grooves on the cap 10, so that the spring 12 cannot rotate back the cap and the scale. The number of clicks indicates the set dose.

The cap is screwed outwards by the setting and is separated from the piston rod 9 which is clutched by the 20 coupling 3, 4 and 28, 29.

Hereafter the cap 18 may be removed and a space member 2 may be placed against the skin whereupon the release button 13 may be actuated.

The hook 5 will be released and the spring 14 will 25 draw the unit and the hook with it down to a stop 27. The needle will now be injected and the cap 10 will be out of engagement with the scale 7 which is set to zero by the spring 12.

The injection is performed by pressing the cap 10 30 against the case 8. Hereafter the apparatus and with it the needle 19 may be withdrawn from the skin and the cap may be put on again, whereupon a compressing of the spring, a setting, and an injection may be performed anew.

When the carpule 1 is empty a normal presetting is 35 performed by rotating the cap 10, and the locking member 16 is removed by being screwed out. Hereafter the cap 10 is pressed forwards whereby a stop (not shown) on the piston rod 9 and/or

the compression spring 33 will affect the ring 3 forwards whereby the arms 4 are coupled free and the carpule may be drawn out. Hereafter a new carpule may be mounted and the mixing may be performed again as described.

5 The method performed by the apparatus of Fig. 1 is in principle identic to the one shown in Fig. 2, but the cap is divided into two, the button 20 being screwed against the piston rod 9 before the mixing.

10 By the method and the apparatus according to the invention the most careful mixing is obtained and the dosing is extremely exact, the optimal medical effect being ensured. Especially by sensitive and expensive hormone preparations this is of decisive importance to the result of the treatment.

CLAIMS

1. A method for mixing a liquid and a medicament in a two-compartment carpule after this carpule has been positioned in a syringe for dosed injection of the mixed product, the
5 carpule comprising a front chamber containing the medicament and being at its front end delimited by a membrane closing the front end of the carpule and being at its rear end closed by a first displaceable piston, and a rear chamber containing the liquid and being at its front end delimited by the first
10 displaceable piston and being at its rear end delimited by a second displaceable piston at the rear end of the carpule, and a passage between the two chambers, which passage may be opened by a joint displacement of the first and the second piston and the liquid between them in a direction toward the front end of
15 the carpule, whereafter a further displacement of the second piston presses the liquid through the passage for mixing with the medicament, characterized in that the carpule is inserted in a tubular housing from the front end thereof, so that a piston rod mounted in the housing and being displaceable in the
20 longitudinal direction thereof is pressed out through the rear end of the housing by abutting the second piston, whereupon a screw stopper carrying a needle is mounted to secure the carpule in the housing and penetrate the membrane, whereafter the piston rod is pressed into the housing to press the rear
25 piston forwards in a direction towards the front end of the carpule until the liquid has been pressed through the passage into the front chamber.

2. An apparatus for mixing a liquid and a medicament according to claim 1 and subsequent injection of the mixture,
30 characterized in that it comprises a housing which may be opened at its front end for inserting a two-compartment carpule being closed by a membrane at its front end and by a piston at its rear end, a piston rod which is displaceable in its longitudinal direction and which is pressed out through the
35 rear end of the housing when the carpule is inserted and which may be passed forwards to actuate the rear piston of the

carpule for mixing the medicament and the liquid and for subsequent injection of the mixture, when the carpule has been secured in the housing by mounting on the front end of the housing a screw stopper carrying a needle for penetrating the 5 membrane of the carpule.

3. An apparatus according to claim 2, characterized in that the piston rod is provided with a withdrawal detent being activated when the carpule is inserted in the housing.

4. Apparatus according to claim 3, characterized in 10 that by injection the forward movement of the piston rod is preset by a pressing part screwed on the rear part of the piston rod, so that the distance between the pressing part and a stop in the housing can be set by rotation and thereby define the movement of the piston rod and thus the dose injected.

15 5. An apparatus according to claim 4, characterized in that the rotation of the pressing part by setting may be read on a scale, which rotates with the pressing part and is set to zero after the injection.

6. An apparatus according to claim 4, characterized 20 in that the piston rod is clutched by a coupling during the rotation of the pressing part.

7. Apparatus according to claim 3, 4 and 6, characterized in that the withdrawal detent and the coupling are provided as holders having arms with teeth engaging backwards 25 facing teeth on the piston rod whereby the piston rod on one side is prevented from being passed backwards when the arms are pressed against the piston rod, and on the other side is prevented from being rotated when the holders engage longitudinal tracks in the piston rod.

1/2

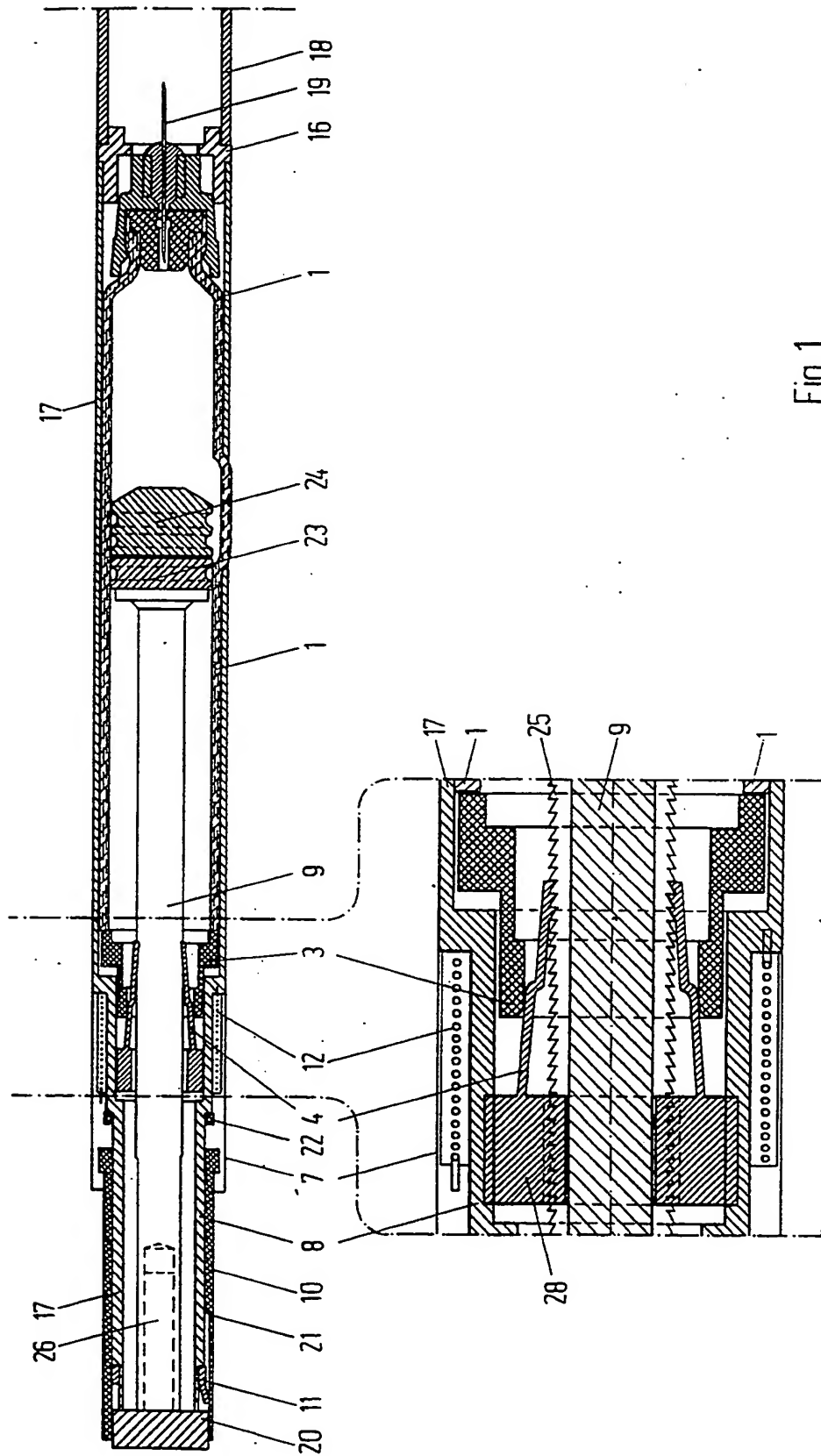


Fig. 1

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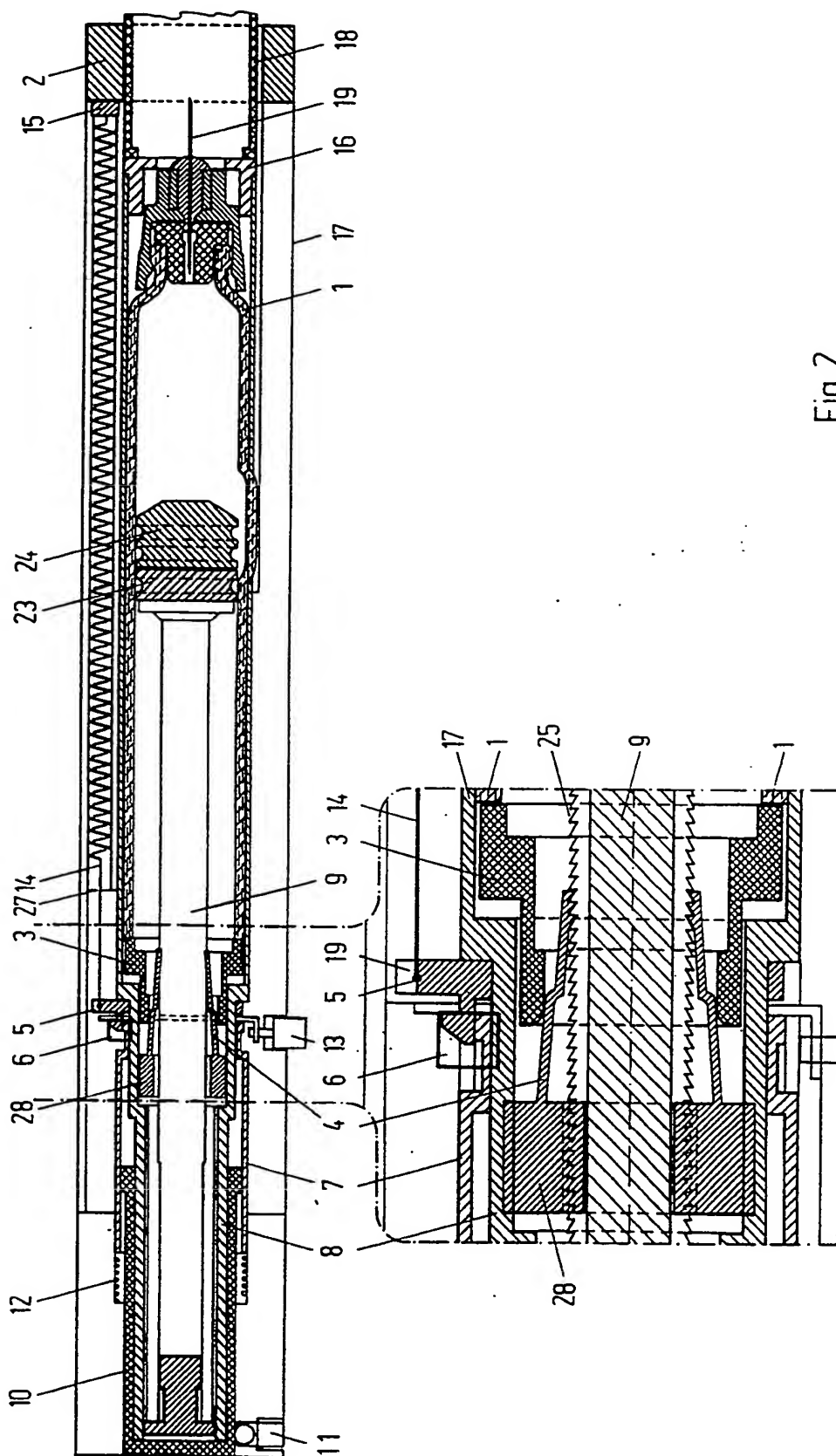


Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No **PCT/DK 91/00012**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 M 5/24, 5/19																				
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border: 1px solid black;">Classification System</th> <th style="border: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border: 1px solid black; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: 1px solid black; vertical-align: bottom;">A 61 M</td> </tr> </table> <div style="border-top: 1px solid black; padding-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <div style="border-top: 1px solid black; padding-top: 10px;">SE,DK,FI,NO classes as above</div>			Classification System	Classification Symbols	IPC5	A 61 M														
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; border: 1px solid black;">Category *</th> <th style="border: 1px solid black;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 10%; border: 1px solid black;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">X</td> <td style="border: 1px solid black; vertical-align: top;">US, A, 2646798 (F.E. BROWN) 28 July 1953, see column 3, line 13 - line 54; column 4, line 25 - column 5, line 68; figures 1-5,9</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-2</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">Y</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">--</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">3-7</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">Y</td> <td style="border: 1px solid black; vertical-align: top;">EP, A2, 0327910 (D.C.P. AF 1988 A/S) 16 August 1989, see column 4, line 38 - column 7, line 15; figures 1-5</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">3-7</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">A</td> <td style="border: 1px solid black; vertical-align: top;">EP, A1, 0298067 (KABIVITRUM AB) 4 January 1989, see column 6, line 35 - line 42; abstract; figure 4</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-2</td> </tr> <tr> <td style="border: 1px solid black; text-align: center; vertical-align: top;">A</td> <td style="border: 1px solid black; vertical-align: top;">US, A, 2607344 (F.E. BROWN) 19 August 1952, see column 1, line 24 - column 2, line 2; figures 1-2</td> <td style="border: 1px solid black; text-align: center; vertical-align: top;">1-2</td> </tr> </tbody> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 2646798 (F.E. BROWN) 28 July 1953, see column 3, line 13 - line 54; column 4, line 25 - column 5, line 68; figures 1-5,9	1-2	Y	--	3-7	Y	EP, A2, 0327910 (D.C.P. AF 1988 A/S) 16 August 1989, see column 4, line 38 - column 7, line 15; figures 1-5	3-7	A	EP, A1, 0298067 (KABIVITRUM AB) 4 January 1989, see column 6, line 35 - line 42; abstract; figure 4	1-2	A	US, A, 2607344 (F.E. BROWN) 19 August 1952, see column 1, line 24 - column 2, line 2; figures 1-2	1-2
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Y	--	3-7																		
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																				
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 15th April 1991 </td> <td style="width: 50%; border: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report 1991-04-23 </td> </tr> <tr> <td style="border: 1px solid black; padding: 5px;"> International Searching Authority <div style="text-align: center; border-top: 1px solid black; padding-top: 5px;"> SWEDISH PATENT OFFICE </div> </td> <td style="border: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; border-top: 1px solid black; padding-top: 5px;"> Folke Svensson </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 15th April 1991	Date of Mailing of this International Search Report 1991-04-23	International Searching Authority <div style="text-align: center; border-top: 1px solid black; padding-top: 5px;"> SWEDISH PATENT OFFICE </div>	Signature of Authorized Officer <div style="text-align: center; border-top: 1px solid black; padding-top: 5px;"> Folke Svensson </div>														
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4613326 (SZWARC) 23 September 1986, see column 8, line 37 - line 68; figure 5 --	1-2
A	US, A, 1604224 (B. FRIEDMAN) 26 October 1926, see page 2, line 44 - line 64; figures 1-4 --	1-2
A	WO, A1, 8807874 (D.C.P. AF 1988 A/S) 20 October 1988, see page 6, line 9 - page 7, line 29; figure 2 -- -----	1-3

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/DK 91/00012**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-03-23
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 2646798	53-07-28	NONE	
EP-A2- 0327910	89-08-16	AU-D- 3066689	89-09-06
		US-A- 4973318	90-11-27
		WO-A- 89/07463	89-08-24
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		SE-A- 8702735	89-01-03
		US-A- 4968299	90-11-06
		SE-A- 8801405	89-10-16
US-A- 2607344	52-08-19	NONE	
US-A- 4613326	86-09-23	AU-B- 581136	89-02-09
		AU-D- 5477686	87-01-15
		CA-A- 1262327	89-10-17
		EP-A- 0208053	87-01-14
		JP-A- 62014863	87-01-23
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		ZA-A- 8802334	88-09-23

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